

PATENT SPECIFICATION

NO DRAWINGS

Inventors: FREDERICK CHARLES COPP and GEOFFREY GEORGE COKER

924961



Date of filing Complete Specification (under Section 3 (3) of the Patents Act, 1949): Feb. 29, 1960.

Application Date: March 13, 1959.

No. 8878/59.

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Application Date: Nov. 20, 1959.

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Index at acceptance:—Class 2(3), C1D, C1E4K(3:4:6:7), C1E7(E1:E2:F2:H2:J:N3:N5:P3), C1F1(A2:C4:D2:D3), C1F2(A1:A2:C4:C6:D2:D3), C1F3(A2:C4:D2:D3), C1F4(A1:A2:C1:C4:D2:D3:F2:F3:F4), C1Q(2:4:6B1:6C:8A:8C:9C:9F1:9G:11D:11G:11J), C2B3(A2:A4:B:C:D:G1:G4:G8), CB2(9:10:17:18:20:30:32), C2B44(C1:E:G3:G7), C3A7V1(A4:E1:E2:G1:G2:K1).

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ERRATA

SPECIFICATION No. 924,961

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Page 1, line 18, for "Toxocari" read "Toxocara"
Page 3, line 77, after "novel." begin new paragraph with "The compounds . . ."
Page 4, line 103, for "II" (second occurrence) read "III"
Page 5, Table, Example 18, for "128—" read "128o"
Page 9, Example 72, for " p_2Cl " read " pCl "
Page 11, Example 100, for " OH_i " read " CH_i "
Page 12, Example 129, for " $-(CH_2)_4-$ " read " $-(CH_2)_4-$ "
Page 12, Example 126, for "122—" read "122o"
Page 19, Example 222, for " $O(CH_2)_4$ " read " $O(CH_2)_3$ "
Page 20, Example 246, for " $-(CH_2)_2-$ " read " $-(CH_2)_4-$ "
Page 22, Table 11, 2nd Column, line 22, for " $OC(H_2)_4$ " read " $O(CH_2)_4$ "
Page 22, Table 11, 2nd Column, line 25, for " $O(CH_2)_4$ " read " $O(CH_2)_5$ "
Page 22, Table 11, 5th Column, line 20, for "0.02" read "0.2"
Page 23, Table 11, 2nd Column, for " $O(CH_2)_6$ " read " $O(CH_2)_6$ "
Page 23, Table 11, 5th Column, line 7, for "0.80" read "0.08"
Page 24, End of Table 11, 2nd line, for "has" read "had"
Page 26, line 69, for "points" read "point"
Page 27, line 13, for "give" read "gave"
Page 27, line 23, for "dimethylammonium" read "dimethylammonium"
Page 28, line 49, for "oxide" read "iodide"
Page 29, lines 38 and 39, for "propared" read "prepared"

THE PATENT OFFICE
4th March 1965

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International Classification:—C07c, d.

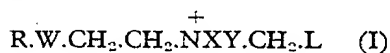
COMPLETE SPECIFICATION

Quaternary Ammonium Compounds, the preparation thereof and Pharmaceutical Compositions thereof

We, THE WELLCOME FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to quaternary ammonium compounds, to the preparation thereof and to pharmaceutical compositions thereof.

It has been found that quaternary ammonium compounds containing a cation of formula (I) effectively decrease infestations of nematodes, for example of *Syphacia obvelata*, *Aspiculuris tetraptera*, or *Trichuris muris* in mice, of *Toxocari cati* in cats, of *Toxocara canis*, *Trichuris vulpis*, or *Ancylostoma caninum* in dogs, or of *Ascaridia galli* in chickens, or kill *Ascaris lumbricoides* from pig in vitro.



In formula (I) and subsequent formulae:

R is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy-carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring optionally substituted in the *ortho*, *meta*, or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group, or when L is a thienyl or furyl group optionally substituted in the 5- position with a halogen atom or a nitro group; or—

R is a phenyl ring optionally substituted in the *ortho* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy-carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group;

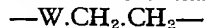
W is a straight saturated chain which contains 1 to 3 non-adjacent oxygen atoms and 0 to 16 carbon atoms; and

X and Y are the same or different and each is an alkyl or allyl group, or XY is a tetramethylene, pentamethylene, or 3 - oxapentamethylene group (that is, the group NXY is a pyrrolidino, piperidino, or morpholino group).

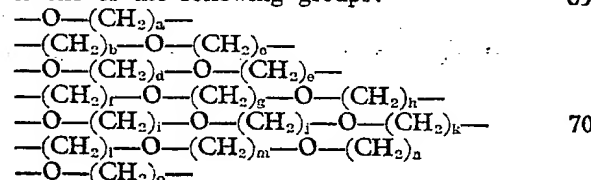
In the above definitions of R, M, X, and Y, "alkyl," "alkoxy," and "alkoxycarbonyl" denote respectively saturated hydrocarbon, ether, and ester groups containing from one to four carbon atoms.

The anion associated with the cation of formula (I) may be the anion equivalent of any pharmaceutically acceptable acid, for example a chloride, bromide, iodide, sulphate, or methylsulphate anion.

It will be seen that the chain



is one of the following groups:



wherein *a*, *b*, *c*, *d*, *e*, *f*, *g*, *h*, *i*, *j*, *k*, *l*, *m*, *n*, and *o* are integers; *a*, *c*, *e*, *h*, *k*, and *o*, are each at least 2; and *a*, or the sum of *b* and *c*, or the sum of *d* and *e*, or the sum of *f* and *g* and *h*, or the sum of *i* and *j* and *k*, or the sum of *l* and *m* and *n* and *o* is not more than 18. For example, —W.CH₂.CH₂— may be a 3 - oxatrimethylene, 8 - oxaoctamethylene, 6-oxadecamethylene, 3,5 - dioxapentamethylene, 7,9 - dioxanonamethylene, 5,8 - dioxadecamethylene, 8,11 - dioxatridecamethylene, 3,5,7 - trioxaheptamethylene, 4,7,10 - trioxadecamethylene, 3,5,7 - trioxaoctamethylene, or 6,9,13 - trioxapentadecamethylene group.

N - 5 - *p* - Chlorophenoxy - 3 - oxapentyl-*N* - *p* - chlorobenzyl - *N,N* - dimethylammonium sulphate and *N* - *p* - *t* - butylphenoxyethoxyethyl - *N* - benzyl - *N,N* - dimethylammonium hydroxide have been named but in no way described; *N* - benzyl-*N* - 5 - *p* - methylphenoxy - 3 - oxapentyl-*N,N* - dimethylammonium - *n* - dodecyl-oxacetate, *N* - benzyl - *N,N* - diethyl - *N* - 2 - *m* - methoxyphenoxyethylammonium chloride, and *N* - benzyl - *N,N* - diethyl - *N* - 2 - *m* - *t* - butoxyphenoxyethylammonium chloride have been described in the literature, but no anthelmintic activity has hitherto been described for these compounds.

The present invention in one aspect provides the quaternary ammonium compounds containing a cation of formula (I), in so far as they are novel.

The preferred compounds for effectively decreasing infestations of *Syphacia obvelata* or *Aspicularis tetraptera* in mice contain a cation of formula (I) wherein R is a *para*-bromophenyl ring, or R is a *para*-chlorophenyl ring and W contains only one oxygen atom; and those for effectively decreasing infestations of *Trichuris muris* in mice contain a cation of formula (I) wherein R is a *para*-nitrophenyl ring. The preferred compounds for killing *Ascaris lumbricoides in vitro* contain an *N* - *p* - nitrobenzyl - *N* - 2 - *p* - nitrophenoxyethylpyrrolidinium or *N* - *p* - chlorobenzyl - *N* - 2 - *p* - chlorophenoxyethylpyrrolidinium cation.

The chain W preferably contains only one oxygen atom and not more than 8 carbon atoms.

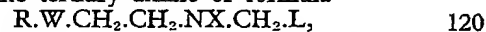
The preferred salts containing a cation of formula (I) are those which are sparingly soluble in water, for example less than 2.0% w/v at 20° C. The anthelmintic activity of the cation is retained whilst the toxic effects on the host are much reduced. Particularly useful salts are those having a borofluoride, perchlorate, laurylsulphate, dodecylbenzenesulphonate, *p* - toluene sulphonate, *p*-chlorobenzenesulphonate, *p* - bromobenzenesulphonate, *p* - acylamidobenzenesulphonate, *N*-acylated amino-acid carboxylate, diphenyl-4-sulphonate, naphthalene - 1 - sulphonate,

naphthalene - 2 - sulphonate, naphthalene-1,5 - disulphonate, naphthalene - 2,7 - disulphonate, 1 - naphthol - 3,6 - disulphonate, 2 - naphthol - 3,6 - disulphonate, 1 - naphthoate, 2 - naphthoate, 2 - hydroxy - 3 - naphthoate, 4,4¹ - dihydroxydiphenylmethane - 3,3¹-dicarboxylate, 2,2¹ - dihydroxy - 1,1¹ - dinaphthylmethane - 3,3¹ - dicarboxylate, piperazine - 1,4 - bis - carbodithioate, 4,4¹ - diamino stilbene - 2,2¹ - disulphonate, or phenate, such as 2,4,5 - trichlorophenate, anion equivalent.

The compounds containing a cation of formula (I) may be prepared by any known method for a quaternising reaction, for instance by the reaction of a tertiary amine containing all but one of the groups desired in the quaternary ammonium compound with a reactive ester of the hydroxy derivative of the group it is desired to introduce.

For example, the compounds may be prepared by the quaternisation of a tertiary amine of formula R.W.CH₂.CH₂.NXY with a reactive benzyl-, furfuryl-, or thenyl- ester or of a tertiary amine of formula XYN.CH₂.L with a reactive R.W.CH₂.CH₂— ester. In these and subsequent reactions, Z is the reactive ester group mentioned above and may be, for example, a chloride, bromide, or iodide, or a sulphonic ester group, —O.SO₂E, wherein E is a substituted or unsubstituted hydrocarbon such as a *p*-tolyl group. Both reactions may conveniently be effected in a solvent, for example propan - 2 - ol or acetone. The former reaction proceeds readily. The reaction mixture of the latter however, requires heating for a prolonged period; it may be effected by heating the compounds of formulae R.W.CH₂.CH₂.Z and XYN.CH₂.L together without the presence of a solvent.

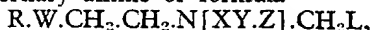
Another example, applicable to compounds wherein X and Y are both aliphatic groups, is the quaternisation of a tertiary amine of formula R.W.CH₂.CH₂.NX.CH₂.L with an alkylating agent of formula YZ. If X and Y are the same, the compounds may also be prepared by the reaction of a secondary amine of formula R.W.CH₂.CH₂.NH.CH₂.L with two equivalents of an alkylating agent of formula YZ, in the presence of an acid binding agent, for example an alkaline salt such as sodium or potassium carbonate; this reaction proceeds with the intermediate formation of the tertiary amine of formula



and therefore amounts to the simultaneous formation of this amine and its quaternisation. As specific examples of alkylating agents which may be used in these reactions, methyl iodide, dimethyl sulphate, methyl *p*-toluenesulphonate, ethyl iodide, and ethyl *p*-toluenesulphonate may be mentioned. In practice, it is generally preferable to use rather more than the theoretically required amount of the alkylating agent to obtain a

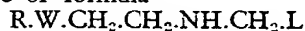
good yield of the desired product. Both reactions may be effected in a solvent, for example, acetone or methanol.

The compounds wherein NXY is a pyrrolidino, piperidino or morpholino group may also be prepared by an internal quaternisation of a tertiary amine of formula



wherein $-XYZ$ is a tetramethylene, pentamethylene, or 3-oxapentamethylene group respectively, carrying the ester group Z terminally. This amine may be prepared, as the salt, by the reaction of the corresponding hydroxy compound (wherein the hydroxy group is terminally attached to XY) of formula $R.W.CH_2.CH_2.N[XY.OH].CH_2.L$ with a halogenating agent, for example with thionyl chloride, hydrobromic acid, or hydriodic acid, or with a sulphonyl chloride such as *p*-toluenesulphonyl chloride. The salt is converted into the free amine base and the internal quaternisation is effected by heating this base either alone, or in a solvent, such as isobutanol or a mixture of benzene and ethanol, the rate of reaction varying with the nature of Z .

The compounds wherein NXY is a pyrrolidino, piperidino, or morpholino group may also be prepared by the reaction of a secondary amine of formula



with an α,ω -disubstituted-butane, -pentane, or -3-oxapentane, of formula $Z.XY.Z$. As specific examples, 1,4-dibromobutane, 1,4-dichlorobutane, 1,4-dimethylsulphonyloxybutane, 1,4-di-*p*-toluenesulphonyloxybutane, 1-bromo-4-chlorobutane, 1,5-di-*p*-toluenesulphonyloxy-pentane, and 1,5-di-*p*-toluenesulphonyloxy-3-oxapentane may be mentioned. The reaction is effected in the presence of an acid binding agent, for example an alkaline salt such as sodium or potassium carbonate, by heating alone or in a solvent such as isobutanol or a mixture of benzene and ethanol. The reaction proceeds with the intermediate formation of the tertiary amine of formula



as defined above, and therefore amounts to the simultaneous formation of this amine and its internal quaternisation.

When R is a phenyl ring carrying a free amino group, it is necessary to modify the above described methods of preparation of the compounds containing a cation of formula (I) by protecting the amino group, for example, with an acyl or alkoxycarbonyl group or a hydrocarbonsulphonyl group, $-SO_2E$, wherein E is as defined above, which is then removed by hydrolysis after the formation of the appropriate quaternary ammonium compound.

The salt produced by the above described reactions may be converted by double decomposition, either during or after the reactions,

for example in solution or an anion exchange column, into the salt of another anion. This may be particularly desirable if a salt which is sparingly soluble in water is required, or if an α,ω -disubstituted compound of formula $Z.XY.Z$ is used and the two Z groups are different.

The present invention in another aspect provides the above described method of preparation of the quaternary ammonium compounds containing a cation of formula (I), in so far as they are novel. The compounds containing a cation of formula (I) may be presented as a solid pharmaceutical composition for oral administration made by any method.

Fine powders or granules of the compounds may contain diluents and dispersing and surface active agents, and may be presented in a draft or drench in water or in a syrup; in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets when binders and lubricants may be included; in a suspension in water or a syrup or an oil, or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included; or in the food of the host of the nematode. The granules or the tablets may be coated.

The present invention in other aspects provides a solid pharmaceutical composition for oral administration containing a quaternary ammonium compound containing a cation of formula (I) and a pharmaceutically acceptable carrier therefor, and the methods for making such a preparation by the inclusion of a quaternary ammonium compound containing a cation of formula (I) in the pharmaceutically acceptable carrier therefor.

The following examples illustrate but do not limit the invention, whose scope is defined in the claims. All temperatures are in degrees Celsius and "b.p." and "m.p." represent respectively boiling point and melting point.

EXAMPLE 1.

A mixture of *p*-nitrophenol (139 g.), 1,4-dibromobutane (259 g.), isopropanol (40 ml.), and water (1 l.) was stirred and heated to reflux whilst a solution of sodium hydroxide (34 g.) in water (300 ml.) was slowly added over a period of 3 hours. The mixture was then stirred for a further 3 hours. After cooling, the aqueous layer was removed and extracted with ether. The combined organic layers were washed 3 times with 2*N*-sodium hydroxide solution to remove unchanged *p*-nitrophenol. The ethereal solution was washed with water, dried over potassium carbonate, filtered, and evaporated. The residue was distilled *in vacuo* to give 1-bromo-4-*p*-nitrophenoxybutane, b.p. 144–146°/0.06 mm.

A solution of this ether (62 g.) in ethanolic dimethylamine (154 g.; 33% w/w) was heated

at 80° for 6 hours in an autoclave. The resulting reaction mixture was evaporated on a steam-bath. The residue was dissolved in excess 4*N* - hydrochloric acid, and the non-

5 basic by-products were removed with ether. Addition of excess ammonia to the acid layer precipitated an oil, which was extracted with ether. The ethereal solution was washed with water, dried over potassium carbonate, 10 filtered, and evaporated. The residual oil was redissolved in excess 4*N* - hydrochloric acid and the solution evaporated *in vacuo*. The residue was crystallised twice from methanol to give 1 - dimethylamino - 4 - *p* - nitro- 15 phenoxybutane hydrochloride, m.p. 173°. The pure base was regenerated with excess ammonia and isolated with ether as a yellow oil which subsequently solidified, m.p. 20°.

20 Benzyl bromide (4 g.) was added to a solution of this base (5 g.) in acetone (10 ml.). The mixture became hot. Finally it was heated to reflux for 30 minutes. On cooling, a crystalline solid rapidly separated. This was collected and recrystallised from isopropanol 25 to give *N* - benzyl - *N,N* - dimethyl - *N* - 4 - *p* - nitrophenoxybutylammonium bromide, m.p. 152°.

EXAMPLE 2.

30 5 - Chlorothenyl chloride (5 - chloro - 2¹-chloromethylthiophen) (4.1 g.) was added to a solution of sodium iodide (3.52 g.) in acetone (10 ml.) and the mixture warmed. After standing for 30 minutes, the precipitated sodium chloride was filtered off and 35 washed with a little fresh acetone. 1 - Dimethylamino - 4 - *p* - nitrophenoxybutane (5.7 g.) was added to the filtrate and the solution heated to reflux for 30 minutes. After cooling, the separated crystalline solid was 40 filtered off and washed with ethyl acetate. The residual *N* - 5 - chloro - thenyl - *N,N* - dimethyl - *N* - 4 - *p* - nitrophenoxybutylammonium iodide was recrystallised from methanol and it then had a melting point of 45 139—140°.

EXAMPLE 3.

50 A solution of 1 - bromo - 2 - *p* - chlorophenoxyethane (7.8 g.) and benzylamine (15 g.) in benzene (15 ml.) was heated on a steam-bath for 5 hours. After cooling, the mixture was filtered and the residue washed with fresh benzene. The combined filtrate and washings were shaken with excess 4*N* - hydrochloric acid, when solid 1 - benzylamino - 2 - *p*-

chlorophenoxyethane hydrochloride separated. 55 This was filtered off and recrystallised from isopropanol containing 10% ethanol, as colourless needles, m.p. 190—191°.

This hydrochloride (5.96 g.) was treated 60 with aqueous ammonia to give the free base which was isolated with ether. This base was added to a slurry of sodium carbonate (5.3 g.) in methanol (15 ml.), followed by methyl iodide (14.5 g.). The resulting mixture was 65 heated to reflux for 2 hours, and filtered hot. Ether was added to the filtrate to give *N* - benzyl - *N* - 2 - *p* - chlorophenoxyethyl-*N,N* - dimethylammonium iodide which was recrystallised from ethanol, as a solid of m.p. 70 166°.

EXAMPLE 4.

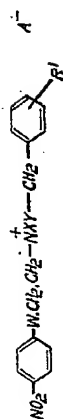
A mixture of 1 - bromo - 2 - *p* - chlorophenoxyethane (20 g.) and benzylmethylamine (22 g.) was warmed to 70°, when a 75 rapid exothermic reaction occurred. After cooling, the semi-solid mass was dissolved in excess dilute hydrochloric acid, and the solution was washed with ether. Treatment with sodium hydroxide, extraction with ether and evaporation of the dried solution gave a basic 80 oil, which was separated by fractional distillation into benzylmethylamine and 1 - benzylmethylamino - 2 - *p* - chlorophenoxyethane, b.p. 158°/0.1 mm.

This base (5 g.) and an equal weight of 85 ethyl *p* - toluenesulphonate were heated in boiling acetone (50 ml.) for three hours. Cooling and addition of ether precipitated *N* - benzyl - *N* - 2 - *p* - chlorophenoxyethyl - *N* - ethyl - *N* - methylammonium *p* - toluenesulphonate, which was crystallised from ethyl 90 acetate and formed colourless plates, m.p. 121—122°.

In Table I are listed further quaternary ammonium compounds which were prepared 95 by methods analogous to those described herein. Tables II and III give the physical properties of those chemical intermediates which were required for the synthesis of the 100 compounds in Table I and which have not previously been described in the scientific literature.

In Tables I, II and II, R², R³, R⁴, and R⁵ indicate the substituents in the rings; in Table 105 I, A⁻ indicates the anion associated with the cation; and in Table III, Z is a reactive ester group.

TABLE I (A)



Example Number	W·CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
5	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Ethanol/methanol	228—229°
6	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Methanol	172—173°
7	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -NO ₂	Cl	Ethanol	199—200°
8	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -NO ₂	I	Ethanol	193—193.5°
9	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —	—(CH ₂) ₂ O(CH ₂) ₂ —	<i>p</i> -NO ₂	I	Methanol	191—192°
10	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Ethanol	202—203°
11	O(CH ₂) ₃	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -NO ₂	I	Methanol	203°
12	O(CH ₂) ₃	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -NO ₂	I	Aqueous methanol	201°
13	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Methanol	225—226°
14	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Ethanol	163—164°
15	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl	Ethanol	183—184°
16	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	I	Methanol	200—201°
17	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —	—(CH ₂) ₂ O(CH ₂) ₂ —	<i>p</i> -Cl	I	Methanol	177—178°
18	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Methanol	127—128°
19	O(CH ₂) ₃	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I, ½ H ₂ O	Ethanol	145—146°
20	O(CH ₂) ₃	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	I	Methanol	175°
21	O(CH ₂) ₃	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	I	Methanol	170—171°

TABLE I (A) (Continued)

Example Number	W. CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
22	O(CH ₂) ₃	-(CH ₂) ₂ O(CH ₂) ₃ -	CH ₃	<i>p</i> -Cl	I	Methanol	199-200°
23	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -Cl	Cl. $\frac{1}{2}$ H ₂ O	Ethanol/ethyl acetate	137°
24	O(CH ₂) ₅	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	158-159°
25	O(CH ₂) ₆	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol/ethyl acetate	157°
26	CH ₃ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	I	Methanol/ethanol	180-182°
27	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -Br	Br	Methanol/ethyl acetate	179-180°
28	O(CH ₂) ₃	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Br	Br	Ethanol	206°
29	O(CH ₂) ₃	-(CH ₂) ₄ -	-(CH ₂) ₄ -	<i>p</i> -Br	Br	Methanol/ether	140°
30	O(CH ₂) ₅	CH ₃	CH ₃	<i>p</i> -Br	Br	Methanol	165°
31	CH ₃ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Br	Br	Ethanol	200-203°
32	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -F	Cl. 2 H ₂ O	Ethanol/ether	85°
33	O(CH ₂) ₃	-(CH ₂) ₄ -	-(CH ₂) ₄ -	<i>p</i> -F	I	Ethanol/methanol	171°
34	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -F	I	Ethanol	165°
35	O(CH ₂) ₅	CH ₃	CH ₃	<i>p</i> -F	I	Ethanol	117°
36	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -I	Br	Aqueous methanol	209°
37	O(CH ₂) ₃	C ₂ H ₅	C ₂ H ₅	<i>p</i> -I	Br	Methanol	220°
38	O(CH ₂) ₃	-(CH ₂) ₄ -	-(CH ₂) ₄ -	<i>p</i> -I	Br	Methanol	208°
39	(OCH ₂) ₅	CH ₃	CH ₃	<i>p</i> -I	Br	Methanol	203°
40	O(CH ₂) ₆	CH ₃	CH ₃	<i>p</i> -I	Br	Methanol	153-154°

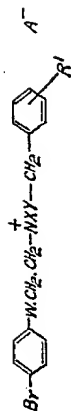
TABLE I (A) (Continued)

Example Number	W. CH_2CH_2	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
41	$\text{O}(\text{CH}_2)_2$	CH_3	CH_3	<i>p</i> -CN	Cl	Methanol	222—223°
42	$\text{O}(\text{CH}_2)_3$	$-(\text{CH}_2)_4-$	$-(\text{CH}_2)_4-$	<i>m</i> -Cl	Br	Ethanol	212°
43	$\text{O}(\text{CH}_2)_2$	CH_3	CH_3	<i>o</i> -Cl	Cl, H_2O	Ethanol/isopropanol	112—113°
44	$\text{O}(\text{CH}_2)_3$	CH_3	CH_3	<i>o</i> -Cl	I	Ethanol	118°
45	$\text{O}(\text{CH}_2)_3$	C_2H_5	C_2H_5	<i>o</i> -Cl	I	Methanol	173—174°
46	$\text{O}(\text{CH}_2)_3$	$-(\text{CH}_2)_4-$	$-(\text{CH}_2)_4-$	<i>o</i> -Cl	I	Methanol	133°
47	$\text{O}(\text{CH}_2)_2$	CH_3	CH_3	H	Br	Ethanol/isopropanol	159—160°
48	$\text{O}(\text{CH}_2)_2$	C_2H_5	C_2H_5	H	Br	Ethanol	139—140°
49	$\text{O}(\text{CH}_2)_2$	$-(\text{CH}_2)_4-$	$-(\text{CH}_2)_4-$	H	Br	Ethanol	164—165°
50	$\text{O}(\text{CH}_2)_2$	$-(\text{CH}_2)_5-$	$-(\text{CH}_2)_5-$	H	I	Methanol	197—198°
51	$\text{O}(\text{CH}_2)_3$	CH_3	CH_3	H	Br	Ethanol/ether	113°
52	$\text{O}(\text{CH}_2)_3$	C_2H_5	C_2H_5	H	Br	Ethanol	130°
53	$\text{O}(\text{CH}_2)_3$	$-(\text{CH}_2)_4-$	$-(\text{CH}_2)_4-$	H	Br	Ethanol	155°
54	$\text{O}(\text{CH}_2)_5$	CH_3	CH_3	H	Br	Ethanol	168—169°
55	$\text{O}(\text{CH}_2)_6$	CH_3	CH_3	H	Br	Ether/isopropanol	112°

$$\text{Ar}^- + \text{H} \begin{array}{c} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{N} \text{---} \text{N} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \\ | \qquad \qquad | \\ \text{C}_6\text{H}_4 \text{---} \text{NO}_2 \qquad \text{C}_6\text{H}_4 \text{---} \text{R}^1 \end{array}$$

Example Number	W. CH ₃ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
55(b)	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Ethanol/methanol	208—209°
56	O(CH ₂) ₂	—(CH ₂) ₄ —		<i>p</i> -NO ₂	Cl. H ₂ O	Isopropanol/ethyl acetate	98— 99°
57	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Isopropanol/ether	185.5—187°
58	O(CH ₂) ₂	—(CH ₂) ₄ —		<i>p</i> -Cl	Cl	Isopropanol/ether	154—155°
59	O(CH ₂) ₂	CH ₃	CH ₃	<i>m</i> -Cl	Br. $\frac{1}{2}$ H ₂ O	Isopropanol	163—164°
60	O(CH ₂) ₂	CH ₃	CH ₃	<i>o</i> -Cl	Cl. H ₂ O	Isopropanol/ether	114—115°
61	O(CH ₂) ₂	CH ₃	CH ₃	H	Cl	Isopropanol/ethyl acetate	164—165°
62	O(CH ₂) ₂	—(CH ₂) ₄ —		H	I	Isopropanol/ethyl acetate	124—125°

TABLE I (C)



Example Number	W.CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
63	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Ethanol	211—212°
64	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Methanol	184°
65	(OCH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -NO ₂	I	Methanol	199°
66	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -NO ₂	Cl, 1/2 H ₂ O	Isopropanol/ether	198°
67	O(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Isopropanol	156—157°
68	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Methanol	214—215°
69	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Methanol	185°
70	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	I	Methanol	170°
71	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	Cl	Ethanol/ether	154°
72	(OCH ₂) ₃	CH ₃	CH ₃	<i>p</i> -Cl	Cl, H ₂ O	Isopropanol/ethyl/acetate	104—105°
73	O(CH ₂) ₃	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Isopropanol/ethanol	166—167°
74	O(CH ₂) ₃	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl, H ₂ O	Isopropanol/ethyl/acetate	145—146°
75	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Isopropanol/ethyl/acetate	176—177°
76	O(CH ₂) ₄	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Isopropanol/ethyl/acetate	150—151°
77	O(CH ₂) ₄	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl, 2H ₂ O	Isopropanol/ether	78—79°

TABLE I (C) (Continued)

Example Number	W. CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
78	O(CH ₂) ₅	CH ₃	CH ₃	<i>p</i> -Cl	Cl.H ₂ O	Isopropanol/ethyl acetate	126—127°
79	O(CH ₂) ₅	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	Cl	Ethanol/ether	140—141°
80	O(CH ₂) ₅	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl.H ₂ O	Isopropanol/ether	157—158°
81	O(CH ₂) ₆	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Isopropanol	160—161°
82	O(CH ₂) ₆	CH ₃	CH ₃	<i>p</i> -Cl	I, $\frac{1}{2}$ H ₂ O	Methanol	190°
83	O(CH ₂) ₆	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	Cl	Isopropanol	169°
84	O(CH ₂) ₆	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl	Isopropanol/ether	101°
85	O(CH ₂) ₁₀	CH ₃	CH ₃	<i>p</i> -Cl	I	Methanol	161—162°
86	O(CH ₂) ₁₀	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	I	Methanol	123°
87	O(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Isopropanol/ether	124—125°
88	O(CH ₂) ₂ O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	I	Isopropanol	133—134°
89	O(CH ₂) ₆	CH ₃	CH ₃	<i>m</i> -Cl	Br	Ethanol	155—156°
90	O(CH ₂) ₆	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>m</i> -Cl	Br	Methanol	141—142°
91	O(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	<i>m</i> -Cl	Br	Isopropanol/ether	93—94°
92	O(CH ₂) ₂	CH ₃	CH ₃	<i>o</i> -Cl	Cl.H ₂ O	Ethanol	127°
93	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>o</i> -Cl	I	Isopropanol	124°
94	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>o</i> -Cl	I	Methanol	159—160°
95	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>o</i> -Cl	I	Methanol	167°

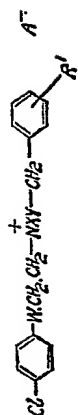
TABLE I (C) (Continued)

Example Number	W.CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
96	O(CH ₂) ₅	C ₂ H ₅	C ₂ H ₅	<i>o</i> -Cl	I	Isopropanol	136—137°
97	O(CH ₂) ₆	CH ₃	CH ₃	<i>o</i> -Cl	Cl	Methanol	178—179°
98	O(CH ₂) ₆	C ₂ H ₅	C ₂ H ₅	<i>o</i> -Cl	I	Ethanol	136—137°
99	O(CH ₂) ₆	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>o</i> -Cl	Cl	Isopropanol/ether	153—154°
100	O(CH ₂) ₅ O(CH ₂) ₂	CH ₃	CH ₃	<i>o</i> -Cl	Cl	Isopropanol/ether	129—130°
101	O(CH ₂) ₂	CH ₃	OH ₃	<i>p</i> -Br	Br	Methanol	226°
102	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Br	Br	Ethanol	195°
103	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Br	Br	Ethanol	176°
104	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Br	Cl	Ethanol/ethyl acetate	156° (softens at 150°)
105	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -CN	I	Methanol	225°
106	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>o</i> -Br	Br	Ethanol/ether	125°
107	O(CH ₂) ₂	CH ₃	CH ₃	H	Br	Methanol	206°
108	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	H	Br	Isopropanol/ether	150—151°
109	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	H	Br	Ethanol	158—159°
110	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	H	Br	Isopropanol	187°
111	O(CH ₂) ₂	CH ₂ CH: CH ₂ CH: CH ₂ CH: CH ₂	CH ₂ CH: CH ₂ CH: CH ₂ CH: CH ₂	H	Br	Acetone/ethyl acetate	115°
112	O(CH ₂) ₂	CH ₃	C ₂ H ₅	H	I	Isopropanol	121—123°
113	O(CH ₂) ₃	CH ₃	CH ₃	H	Cl.H ₂ O	Isopropanol/ethyl acetate	118—119°

TABLE I (C) (Continued)

Example Number	W. CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
114	O(CH ₂) ₃	C ₂ H ₅	C ₂ H ₅	H	I	Isopropanol/ethanol	140—141°
115	O(CH ₂) ₃	—(CH ₂) ₄ —		H	Cl ₂ H ₂ O	Isopropanol/ethyl acetate	78—79°
116	O(CH ₂) ₄	CH ₃	CH ₃	H	Cl ₂ H ₂ O	Isopropanol/ethyl acetate	150—151°
117	O(CH ₂) ₄	C ₂ H ₅	C ₂ H ₅	H	I	Isopropanol	142—143°
118	O(CH ₂) ₄	—(CH ₂) ₄ —		H	Cl ₂ H ₂ O	Isopropanol/ether	91—92°
119	O(CH ₂) ₅	CH ₃	CH ₃	H	Cl ₂ H ₂ O	Isopropanol/ethyl acetate	167—168°
120	O(CH ₂) ₅	C ₂ H ₅	C ₂ H ₅	H	Cl	Isopropanol/ethyl acetate	199—200°
121	O(CH ₂) ₅	—(CH ₂) ₄ —		H	Cl ₂ H ₂ O	Isopropanol/ether	105—106°
122	O(CH ₂) ₆	CH ₃	CH ₃	H	Br	Ethanol	157—158°
123	Q(CH ₂) ₆	C ₂ H ₅	C ₂ H ₅	H	Br	Ethanol	139—140°
124	O(CH ₂) ₆	—(CH ₂) ₄ —		H	Br	Isopropanol	145°
125	O(CH ₂) ₁₀	CH ₃	CH ₃	H	Br	Ethanol	125°
126	(OCH ₂) ₁₀	C ₂ H ₅	C ₂ H ₅	H	Br	Ethanol/ether	121—122°
127	(OCH ₂) ₁₀	—(CH ₂) ₄ —		H	Br	Ethanol/ethyl acetate	115—118°
128	O(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	H	Cl	Isopropanol/ether	119—120°
129	O(CH ₂) ₂ O(CH ₂) ₂	—CH ₂) ₄ —		H	I	Isopropanol	124—125°

TABLE I (D)

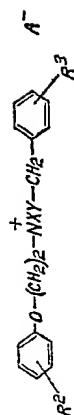


Example Number	W, CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
130	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Methanol	229—230°
131	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I, 1.2H ₂ O	Methanol	164—165°
132	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -NO ₂	Cl, 2H ₂ O	Isopropanol/ether	175°
133	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -NO ₂	Cl	Ethanol/ether	194°
134	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —	—(CH ₂) ₂ O(CH ₂) ₂ —	<i>p</i> -NO ₂	I	Water	187°
135	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	228—229°
136	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Ethanol	186—187°
137	O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl, 1.2H ₂ O	<i>n</i> -Butanol/ether	156°
138	O(CH ₂) ₂	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	Cl	Isopropanol/ether	189°
139	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —	—(CH ₂) ₂ O(CH ₂) ₂ —	<i>p</i> -Cl	I, 1.2H ₂ O	Ethanol	197°
140	CH ₂ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Cl	I	Ethanol	178—181°
141	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -Br	Br	Methanol	232—233°
142	O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -I	Br	Methanol	223—224°

TABLE I (D) (Continued)

Example Number	W.CH ₂ CH ₂	X	Y	R ¹	A ⁻	Solvent for crystallisation	m.p.
143	O(CH ₂) ₂	—(CH ₂) ₄ —		<i>p</i> -CN	I	Ethanol	189—192°
144	CH ₃ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -CN	I	Ethanol	147—150°
145	O(CH ₂) ₂	CH ₃	CH ₃	<i>o</i> -Cl	Cl	Ethanol/ether	115—117°
146	O(CH ₂) ₂	—(CH ₂) ₄ —		<i>o</i> -Cl	Cl.H ₂ O	n-Butanol/ether	84—85°
147	O(CH ₂) ₂	—(CH ₂) ₆ —		<i>o</i> -Cl	I	Methanol	151°
148	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —		<i>o</i> -Cl	Cl ₂ .H ₂ O	Methanol	142°
149	O(CH ₂) ₂	CH ₃	CH ₃	H	Br	Ethanol	194—195°
150	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	H	Br	Ethanol	137—138°
151	O(CH ₂) ₂	—(CH ₂) ₄ —		H	Br	Ethanol/ether	124°
152	O(CH ₂) ₂	—(CH ₂) ₆ —		H	Br	Ethanol	184°
153	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —		H	Br	Ethanol/ether	178—179°
154	O(CH ₂) ₂	CH ₃	C ₃ H ₇	H	I	Ether/ethyl acetate	128—130°
155	O(CH ₂) ₂	CH ₃	CH ₂ .CH: CH ₃	H	I	Isopropanol	106—108°
156	CH ₃ O(CH ₂) ₂	CH ₃	CH ₃	H	I	Ethanol	149—151°

TABLE I (E)



Example Number	Nature and Position of R ²	X	Y	Nature and Position of R ³	A ⁻	Solvent for crystallisation	m.p.
157	<i>p</i> -CN	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Methanol	196—198° (decomposition)
158	<i>p</i> -CN	C ₂ H ₅	C ₂ H ₅	<i>p</i> -CN	I	Methanol	189—193°
159	<i>p</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Methanol	217—218°
160	<i>p</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	222—223°
161	<i>p</i> -CH ₃	CH ₃	CH ₃	<i>o</i> -Cl	Cl·H ₂ O	Ethanol	110—112°
162	<i>p</i> -CH ₃	CH ₃	CH ₃	H	Br	Ethanol	147—148°
163	<i>p</i> -CH ₃ O	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Ethanol	177—178°
164	<i>p</i> -CH ₃ O	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	167—168°
165	<i>p</i> -CH ₃ O	CH ₃	CH ₃	<i>o</i> -Cl	Cl·H ₂ O	Isopropanol/ethyl acetate	82—83°
166	<i>p</i> -CH ₃ O	CH ₃	CH ₃	H	I	Ethanol	135—136°
167	<i>p</i> -CH ₃ CONH	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	183—184°
168	<i>p</i> -CHO	CH ₃	CH ₃	<i>p</i> -NO ₂	I	Methanol	205—208°
169	<i>p</i> -CH ₃ CO	CH ₃	CH ₃	<i>p</i> -NO ₂	I	Ethanol	177—178°
170	<i>p</i> -CH ₃ CO	CH ₃	CH ₃	H	I	Ethanol	122—123°
171	<i>p</i> -CH ₃ OCO	—(CH ₂) ₂ O(CH ₂) ₂ —		<i>p</i> -NO ₂	I	Methanol	168—170°

TABLE I (E) (Continued)

Example Number	Nature and Position of R ²	X	Y	Nature and Position of R ³	A ⁻	Solvent for crystallisation	m.p.
172	<i>p</i> -C ₂ H ₅ O.CO	-(CH ₂) ₅ -		H	I	Ethanol/ethyl acetate	130—132°
173	<i>p</i> -OH	CH ₃	CH ₃	H	I	Ethanol	178—180°
174	<i>m</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Ethanol	178—179°
175	<i>m</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -Cl	I	Methanol	169—170°
176	<i>m</i> -CH ₃	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	Cl	Isopropanol	154—155°
177	<i>m</i> -CH ₃	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	Cl	Isopropanol	202—203°
178	<i>m</i> -CH ₃	CH ₃	CH ₃	<i>o</i> -Cl	Cl.H ₂ O	Isopropanol	93—94°
179	<i>m</i> -CH ₃	C ₂ H ₅	C ₂ H ₅	H	Br	Ethanol	124—125°
180	<i>m</i> -CH ₃ O	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	173—174°
181	<i>m</i> -CH ₃ O	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Isopropanol	147—148°
182	<i>m</i> -CH ₃ O	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	Cl	Ethanol/isopropanol	159—161°
183	<i>m</i> -CH ₃ O	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	Cl	Ethanol/isopropanol	177—178°
184	<i>m</i> -CH ₃ O	-(CH ₂) ₄ -	-(CH ₂) ₄ -	<i>p</i> -NO ₂	Cl	Ethanol	158—159°
185	<i>m</i> -CH ₃ O	-(CH ₂) ₄ -	-(CH ₂) ₄ -	<i>p</i> -Cl	Cl	Ethanol/isopropanol	161—162°
186	<i>m</i> -CH ₃ O	CH ₃	CH ₃	<i>o</i> -Cl	Cl	Isopropanol	150—151°
187	<i>m</i> -CH ₃ O	CH ₃	CH ₃	H	I	Ethanol	130—131°
188	<i>m</i> -CH ₃ O	-(CH ₂) ₄ -	-(CH ₂) ₄ -	H	Br	Isopropanol/ethyl acetate	95—96°
189	<i>o</i> -NO ₂	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Methanol	219—220°

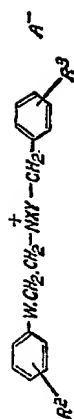
TABLE I (E) (Continued)

Example Number	Nature and Position of R ²	X	Y	Nature and Position of R ³	A ⁻	Solvent for crystallisation	m.p.
190	<i>o</i> -NO ₂	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	173—174°
191	<i>o</i> -Cl	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Methanol/ether	191°
192	<i>o</i> -Cl	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Isopropanol/ether	178—179°
193	<i>o</i> -Cl	CH ₃	C ₂ H ₅	<i>p</i> -NO ₂	I	Ethanol	152—154°
194	<i>o</i> -Cl	CH ₃	C ₂ H ₅	<i>p</i> -Cl	I	Isopropanol	129—132°
195	<i>o</i> -Cl	CH ₃	C ₂ H ₅	<i>p</i> -CN	I	Ethanol	197—199°
196	<i>o</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl·H ₂ O	Ethanol	167—168°
197	<i>o</i> -CN ₃	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	179—180°
198	<i>o</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -Cl	<i>p</i> -CH ₃ ·C ₆ H ₄ ·SO ₃	Isopropanol	165—166°
199	<i>o</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -Br	Br	Ethanol	160—161°
200	<i>o</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -I	Br	Ethanol	182—183°
201	<i>o</i> -CH ₃	CH ₃	CH ₃	<i>p</i> -CN	I	Methanol	214—215°
202	<i>o</i> -CH ₃ O	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Ethanol	133—134°
203	<i>p</i> -CH ₃ O	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Isopropanol	131—132°
204	<i>o</i> -CH ₃ O	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Isopropanol	127—128°
205	H	CH ₃	CH ₃	<i>p</i> -NO ₂	I	Methanol	177—178°
206	H	CH ₃	CH ₃	<i>p</i> -F	Br	Ethanol	145—146°
207	H	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol/ether	191°

TABLE I (E) (Continued)

Example Number	Nature and Position of R ²	X	Y	Nature and Position of R ³	A ⁻	Solvent for crystallisation	m.p.
208	H	CH ₃	CH ₃	<i>p</i> -Br	Br	Ethanol	179—180°
209	H	CH ₃	CH ₃	<i>p</i> -I	Br	Isopropanol	157—158°
210	H	CH ₃	CH ₃	<i>p</i> -CN	I	Ethanol	169—172°
211	H	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Ethanol	149—150°
212	H	C ₂ H ₅	C ₂ H ₅	<i>p</i> -F	Br	Ethanol/isopropanol	148—149°
213	H	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	Cl	Ethanol/isopropanol	199—200°
214	H	C ₂ H ₅	C ₂ H ₅	<i>p</i> -Cl	I	Ethanol	146—147°
215	H	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Ethanol	123—124°
216	H	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -NO ₂	Cl	Isopropanol	169—170°
217	H	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -Cl	Cl	Isopropanol	176—177°
218	H	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -NO ₂	Cl	Isopropanol	165—166°
219	H	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	Cl	Ether/isopropanol	179—179.5°
220	H	CH ₃	CH ₃	<i>m</i> -CH ₃	I	Ethanol	139—140°

TABLE I (F)

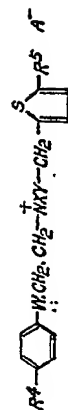


Example number	Nature and position of R ²	WCH ₂ CH ₂	X	Y	Nature and position of R ³	A ⁻	Solvent for crystallisation	m.p.
220	<i>p</i> -CN	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	I	Ethanol	167—169°
221	<i>o</i> -CH ₃	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Isopropanol	113—114°
222	<i>o</i> -CH ₃	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -Cl	Cl·½H ₂ O	Methanol/ether	108—109°
223	<i>o</i> -CH ₃	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Isopropanol	153—154°
224	<i>o</i> -CH ₃	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -Cl	Cl·½H ₂ O	Isopropanol/ether	105—106°
225	<i>o</i> -CH ₃	O(CH ₂) ₃	CH ₃	CH ₃	<i>m</i> -Cl	Br·½H ₂ O	Isopropanol/ether	102—103°
226	<i>o</i> -CH ₃	(OCH ₂) ₄	CH ₃	CH ₃	<i>m</i> -Cl	Br	Isopropanol	126—127°
227	H	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Isopropanol/ether	160—161°
228	H	CH ₂ O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -NO ₂	Cl	Isopropanol	176—177°
229	H	(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	<i>p</i> -NO ₂	I	Ethanol	111—114°
230	H	(CH ₂) ₂ O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	<i>p</i> -NO ₂	I	Isopropanol	64— 67°
231	H	(CH ₂) ₂ O(CH ₂) ₂	—(CH ₂) ₄ —	—(CH ₂) ₄ —	<i>p</i> -NO ₂	I	Ethanol	154—156°
232	H	O(CH ₂) ₃	CH ₃	CH ₃	<i>p</i> -Cl	I	Ethanol	130—131°
233	H	O(CH ₂) ₃	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	I	Methanol	209°
234	H	O(CH ₂) ₄	CH ₃	CH ₃	<i>p</i> -Cl	Cl	Ethanol	200°
235	H	O(CH ₂) ₄	—(CH ₂) ₅ —	—(CH ₂) ₅ —	<i>p</i> -Cl	I·½H ₂ O	Ethanol	113°

TABLE I (F) (Continued)

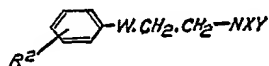
Example number	Nature and position of R^2	WCH_2CH_2	X	Y	Nature and position of R^3	A ⁻	Solvent for crystallisation	m.p.
236	H	$CH_3O(CH_2)_2$	CH_3	CH_3	<i>p</i> -Cl	Cl	Isopropanol/ethylacetate	174—175°
237	H	$CH_3O(CH_2)_3$	CH_3	CH_3	<i>p</i> -Cl	I	Isopropanol	91—94°
238	H	$CH_3O(CH_2)_3$	C_2H_5	C_2H_5	<i>p</i> -Cl	I	Isopropanol	128—131°
239	H	$(CH_2O(CH_2)_4$	CH_3	CH_3	<i>p</i> -Cl	I	Isopropanol	98—101°
240	H	$(CH_2)_2O(CH_2)_2$	C_2H_5	C_2H_5	<i>p</i> -Cl	I	Ethanol	104—106°
241	H	$(CH_2)_3O(CH_2)_2$	$-(CH_2)_4-$	$-(CH_2)_4-$	<i>p</i> -Cl	I	Isopropanol	104—106°
242	H	$CH_3O(CH_2)_2$	CH_3	CH_3	<i>p</i> -CN	I	Isopropanol	120—123°
243	H	$CH_3O(CH_2)_2$	C_2H_5	C_2H_5	<i>p</i> -CN	I	Methanol	197—200°
244	H	$CH_3O(CH_2)_2$	CH_3	C_2H_5	<i>p</i> -CN	I	Isopropanol	105—108°
245	H	$CH_3O(CH_2)_4$	CH_3	CH_3	<i>p</i> -CN	I	Ethanol	144—146°
246	H	$(CH_2)_3O(CH_2)_2$	$-(CH_2)_2-$	$-(CH_2)_2-$	<i>p</i> -CN	I	Isopropanol	114—116°
247	H	$O(CH_2)_3$	CH_3	CH_3	<i>m</i> -Cl	Br	50% Ethanol/isopropanol	175—176°

TABLE I (G)



Example Number	R ⁴	WCH ₂ CH ₂	X	Y	R ⁵	A ⁻	Solvent for Crystallisation	m.p.
248	Cl	O(CH ₂) ₃	CH ₃	CH ₃	H	Cl	Isopropanol	142°
249	Cl	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	H	I	Ethanol	160°
250	Br	O(CH ₂) ₂	CH ₃	CH ₃	H	Cl	Ethanol/ether	179—180°
251	Br	O(CH ₂) ₂	—(CH ₂) ₅ —		H	I	Methanol	196—199°
252	Br	O(CH ₂) ₂	CH ₃	CH ₃	Cl	Cl	Ethanol/ether	195—196°
253	Br	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	Cl	Cl·H ₂ O	Isopropanol	114°
254	Br	O(CH ₂) ₂	—(CH ₂) ₄ —		Cl	I	Methanol	179—180°
255	Br	O(CH ₂) ₂	—(CH ₂) ₅ —		Cl	Cl	Ethanol/ether	202—203°
256	NO ₂	O(CH ₂) ₂	CH ₃	CH ₃	Cl	I	Methanol	158—159°
256 (b)	NO ₂	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	Cl	I	Methanol	139—140°
257	NO ₂	O(CH ₂) ₃	CH ₃	CH ₃	Cl	I	Methanol	160—161°
258	NO ₂	O(CH ₂) ₃	C ₂ H ₅	C ₂ H ₅	Cl	I	Methanol	164°
259	NO ₂	O(CH ₂) ₃	—(CH ₂) ₄ —		Cl	I	Ethanol	152°
260	NO ₂	O(CH ₂) ₄	CH ₃	CH ₃	Cl	I	Methanol	139—140°

TABLE II Intermediate Amines



Nature and Position of R^2	WCH_2CH_2	X	Y	b.p.
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_2$	$-(\text{CH}_2)_5-$		Not distilled
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_3$	CH_3	CH_3	Not distilled
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_3$	C_2H_5	C_2H_5	Not distilled
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_3$	$-(\text{CH}_2)_4-$		Not distilled
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_3$	$-(\text{CH}_2)_5-$		168—194°/0.001 m.m.
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_4$	CH_3	CH_3	Not distilled m.p. $\sim 20^\circ$
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_5$	CH_3	CH_3	Not distilled; m.p. 35°
$p\text{-NO}_2$	$\text{O}(\text{CH}_2)_6$	CH_3	CH_3	Not distilled; m.p. 35°
$p\text{-NO}_2$	$\text{CH}_2\text{O}(\text{CH}_2)_2$	CH_3	CH_3	110—112°/0.05 m.m.
$m\text{-NO}_2$	$\text{O}(\text{CH}_2)_2$	CH_3	CH_3	101—105°/0.01 m.m.
$m\text{-NO}_2$	$\text{O}(\text{CH}_2)_2$	$-(\text{CH}_2)_4-$		128—135°/0.01 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_2$	CH_3	CH_3	150—152°/15 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_2$	C_2H_5	C_2H_5	104—108°/0.1 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_2$	$\text{CH}_2\cdot\text{CH}:\text{CH}_2$	$\text{CH}_2\cdot\text{CH}:\text{CH}_2$	114—118°/0.07 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_2$	$-(\text{CH}_2)_4-$		116°—120°/0.1 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_2$	$-(\text{CH}_2)_5-$		124—128°/0.06 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_3$	CH_3	CH_3	94—98°/0.02 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_3$	C_2H_5	C_2H_5	108—111°/0.1 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_3$	$-(\text{CH}_2)_4-$		108—112°/0.01 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_4$	CH_3	CH_3	98—105°/0.15 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_4$	C_2H_5	C_2H_5	111—117°/0.08 m.m.
$p\text{-Br}$	$\text{OC}(\text{H}_2)_4$	$-(\text{CH}_2)_4-$		113—119°/0.05 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_5$	CH_3	CH_3	105—110°/0.08 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_5$	C_2H_5	C_2H_5	118—122°/0.01 m.m.
$p\text{-Br}$	$\text{O}(\text{CH}_2)_5$	$-(\text{CH}_2)_4-$		126—131°/0.06 m.m.

TABLE II Intermediate Amines (Continued)

Nature and Position of R ²	WCH ₂ CH ₂	X	Y	b.p.
<i>p</i> -Br	O(CH ₂) ₆	CH ₃	CH ₃	108—115°/0.01 m.m.
<i>p</i> -Br	O(CH ₂) ₆	C ₂ H ₅	C ₂ H ₅	120—125°/0.02 m.m.
<i>p</i> -Br	O(CH ₂) ₆	—(CH ₂) ₄ —		128—132°/0.02 m.m.
<i>p</i> -Br	O(CH ₂) ₁₀	CH ₃	CH ₃	162—170°/0.2 m.m.
<i>p</i> -Br	O(CH ₂) ₁₀	C ₂ H ₅	C ₂ H ₅	172°/0.25 m.m.
<i>p</i> -Br	O(CH ₂) ₁₀	—(CH ₂) ₄ —		176—186°/0.15 m.m.
<i>p</i> -Br	O(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	136—138°/0.80 m.m.
<i>p</i> -Br	O(CH ₂) ₂ O(CH ₂) ₂	—(CH ₂) ₄ —		160—164°/0.7 m.m.
<i>p</i> -Cl	O(CH ₂) ₂	CH ₃	CH ₃	139—145°/16 m.m.
<i>p</i> -Cl	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	160—180°/30 m.m.
<i>p</i> -Cl	O(CH ₂) ₂	—(CH ₂) ₄ —		107—110°/0.4 m.m.
<i>p</i> -Cl	O(CH ₂) ₂	—(CH ₂) ₅ —		176—178°/13 m.m.
<i>p</i> -Cl	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —		120—125°/0.15 m.m.
<i>p</i> -Cl	CH ₂ O(CH ₂) ₂	CH ₃	CH ₃	144—150°/10 m.m.
<i>p</i> -CN	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	120—126°/0.2 m.m.
<i>p</i> -CH ₃ CONH	O(CH ₂) ₂	CH ₃	CH ₃	Not distilled
<i>p</i> -CHO	O(CH ₂) ₂	CH ₃	CH ₃	108°/0.2 m.m.
<i>p</i> -CH ₃ O.CO	O(CH ₂) ₂	—(CH ₂) ₂ O(CH ₂) ₂ —		166°/0.05 m.m.
<i>p</i> -C ₂ H ₅ O.CO	O(CH ₂) ₂	—(CH ₂) ₅ —		160—165°/0.1 m.m.
<i>p</i> -CH ₃	O(CH ₂) ₂	CH ₃	CH ₃	121°/16 m.m.
<i>m</i> -CH ₃	O(CH ₂) ₂	CH ₃	CH ₃	119°/12 m.m.
<i>m</i> -CH ₃	O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	141°/17 m.m.
<i>m</i> -CH ₃ O	O(CH ₂) ₂	CH ₃	CH ₃	85—87°/0.08 m.m.
<i>m</i> -CH ₃ O	O(CH ₂) ₂	—(CH ₂) ₄ —		104°/0.05 m.m.
<i>o</i> -CH ₃	O(CH ₂) ₃	CH ₃	CH ₃	128—132°/16 m.m.
<i>o</i> -CH ₃	O(CH ₂) ₄	CH ₃	CH ₃	143—148°/15 m.m.
H	O(CH ₂) ₂	C ₃ H ₇	C ₃ H ₇	140—142°/17 m.m.

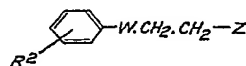
TABLE II Intermediate Amines (Continued)

Nature and Position of R ²	WCH ₂ CH ₂	X	Y	b.p.
H	O(CH ₂) ₂		—(CH ₂) ₄ —	91—92°/0.05 m.m.
H	O(CH ₂) ₃		—(CH ₂) ₅ —	110—114°/0.5 m.m.
H	O(CH ₂) ₄		(CH ₂) ₅	102—106°/0.05 m.m.
H	CH ₂ O(CH ₂) ₂	CH ₃	C ₂ H ₅	135—140°/15 m.m.
H	CH ₂ O(CH ₂) ₄	CH ₃	CH ₃	102—106°/0.5 m.m.

1-Benzylamino-2-*m*-methoxyphenoxyethane had a b.p. 176—182°/0.5 m.m.

1-(*N*-methyl-*N*-*m*-methylbenzylamino)-2-phenoxyethane has a b.p. 124—128°/0.1 m.m.

TABLE III Intermediate Ethers



Nature and position of R ²	WCH ₂ CH ₂	Z	B.p.	m.p.
<i>p</i> -NO ₂	O(CH ₂) ₄	Br	50—156°/0.08 m.m.	—
<i>p</i> -NO ₂	O(CH ₂) ₅	Br	170—171°/0.1 m.m.	—
<i>p</i> -NO ₂	O(CH ₂) ₆	Br	170—210°/0.08 m.m.	—
<i>m</i> -NO ₂	O(CH ₂) ₂	Br	—	40—40.5°
<i>p</i> -Br	O(CH ₂) ₄	Br	118—125°/0.1 m.m.	28—29°
<i>p</i> -Br	O(CH ₂) ₅	Br	123—130°/0.09 m.m.	33—34°
<i>p</i> -Br	O(CH ₂) ₆	Br	132—139°/0.07 m.m.	41—42°
<i>p</i> -Br	O(CH ₂) ₁₀	Br	160—180°/0.15 m.m.	—
<i>p</i> -Br	O(CH ₂) ₂ O(CH ₂) ₂	Cl	148—152°/0.6 m.m.	—
<i>m</i> -CH ₃ O	O(CH ₂) ₂	Br	158—166°/23 m.m.	—
<i>o</i> -CH ₃	O(CH ₂) ₃	Br	138—146°/16 m.m.	—
<i>o</i> -CH ₃	O(CH ₂) ₄	Br	160—168°/15 m.m.	—

EXAMPLE 261.

A solution of *N*-*o*-chlorobenzyl - *N*-2-*p*-chlorophenoxy - ethyl - *N,N*-dimethylammonium chloride (Example 145) (250 g.)

in water (500 ml.) was slowly added to a solution of sodium *p*-toluenesulphonate (191 g.) in water (400 ml.) with stirring. A crystalline solid separated as the addition proceeded. Fin-

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ally the mixture was stood for 17 hours and then filtered. The residue was washed with water and recrystallised from a mixture of isopropanol and ether to give *N* - *o* - chlorobenzyl - *N* - 2 - *p* - chlorophenoxyethyl-*N,N*-dimethylammonium *p*-toluenesulphonate, m.p. 146—147°.

EXAMPLE 262.

By methods analogous is those described in Example 261 *N* - *p* - chlorobenzyl - *N,N*-dimethyl - *N* - 2 - *p* - nitrophenoxyethylammonium chloride (Example 43) was converted into the following salts:

- (i) *p* - chlorobenzenesulphonate, m.p. 238—239°; solubility at 20° approximately 0.1% w/v;
- (ii) *p* - toluenesulphonate, m.p. 226—227°; solubility at 20° approximately 0.2% w/v;
- (iii) 4,4' - diaminostilbene - 2,2' - disulphonate monohydrate, m.p. 181—182°; solubility at 20° approximately 0.1% w/v;
- (iv) 2 - hydroxy - 3 - naphthoate, m.p. 129—130°; solubility at 20° approximately 0.1% w/v;
- (v) embonate monohydrate, m.p. 185—186°; solubility at 20° approximately 0.1% w/v;
- (vi) iodide, m.p. 201—202°; solubility at 20° approximately 0.2% w/v; and
- (vii) 2,4,5 - trichlorophenate, m.p. 154—155°.

EXAMPLE 263.

A solution of *p* - hydroxyacetophenone (100 g.) in ethanol (100 ml.) was added gradually to a solution of sodium (16.9 g.) in ethanol (500 ml.). Ethylene dibromide (174 g.; 25% excess) was then added. The mixture was heated to reflux for 5 hours, cooled, and then poured into water. The oil was extracted with ether and the extract was exhaustively washed with 2*N* - sodium hydroxide solution. The ethereal solution was dried over anhydrous potassium carbonate, filtered, and evaporated. The residue was distilled *in vacuo* to give *p* - 2 - bromoethoxyacetophenone, b.p. 128—136°/0.2 mm. It subsequently solidified, freezing point 55°.

A solution of this compound (20 g.) in ethanol (10 ml.) was added to alcoholic dimethylamine (33% w/w; 56 g.). The mixture was slowly warmed to 60° for 6 hours and then evaporated on a steam-bath. Excess 2*N* - hydrochloric acid was added to the residue and the insoluble oil removed with ether. The acid solution was treated with excess concentrated ammonia and the separated oil extracted with ether. The ethereal extract was dried over potassium carbonate, filtered, and evaporated. The residue was distilled *in vacuo* to give *p* - 2 - dimethyl-

aminoethoxyacetophenone, b.p. 128—132°/0.25 mm.

Finely powered potassium iodide (3.86 g.) was added to a solution of *p*-chlorobenzyl chloride (3.8 g.) in acetone (5 ml.), followed by *p* - 2 - dimethylaminoethoxyacetophenone (4.0 g.). The mixture was heated to reflux for 1.5 hours. After cooling the mixture of solids was filtered off, washed with ethyl acetate, and ground up with water to remove inorganic material. The insoluble solid was filtered off, washed with fresh water, and repeatedly crystallised from ethanol to give *N*-2 - *p* - acetylphenoxyethyl - *N* - *p* - chlorobenzyl - *N,N* - dimethylammonium iodide, m.p. 133—134°.

EXAMPLE 264.

A mixture of *p*-cyanophenol (14.3 g.), 2-chloroethyldimethylamine hydrochloride (23 g.) and sodium hydroxide flake (12.8 g.) was heated and stirred in boiling toluene (100 ml.) for 20 hours. The cooled mixture was extracted with dilute hydrochloric acid, and the extracts were washed with ether. Treatment of the acid extracts with sodium hydroxide solution liberated 2 - *p* - cyanophenoxyethyl-dimethylamine as an oil, which was isolated by means of ether and distilled, b.p. 108—110°/0.2 mm.

Treatment of the base (3.3 g.) with an excess of *p* - cyanobenzyl iodide (6.5 g.) in boiling acetone (50 ml.) yielded *N* - *p* - cyanobenzyl - *N* - 2 - *p* - cyanophenoxyethyl-*N,N* - dimethylammonium iodide, which was crystallised from methanol as colourless prisms, m.p. 213—214°.

EXAMPLE 265.

Sodium metal (3.25 g.) was dissolved in dry ethanol (60 ml.), and a solution of ethyl *p* - hydroxybenzoate (10 g.) in ethanol (25 ml.) was added, followed immediately by a suspension of *N* - 2 - chloroethylmorpholine hydrochloride (15 g.) in the same solvent (50 ml.). The mixture was boiled under reflux for two hours and kept overnight. After filtration from precipitated salts, the alcohol was evaporated, water was added, and the solution was basified with ammonia in the presence of ice. Extraction with chloroform and distillation gave *N* - 2 - *p* - ethoxycarbonylphenoxyethylmorpholine as a viscous oil, b.p. 178°/0.2 mm.

On reaction with *p* - chlorobenzyl iodide (7.5 g.) in acetone (50 ml.), this base (5.0 g.) yielded *N* - *p* - chlorobenzyl - *N* - 2 - *p* - ethoxycarbonylphenoxyethylmorpholinium iodide, which formed needles, m.p. 157—158°, when crystallised from a mixture of ethanol and ethyl acetate.

EXAMPLE 266.

1 - Bromo - 2 - phenoxyethane (30 g.) was added to a solution of *p* - methylbenzylamine

(40 g.) in benzene (100 ml.). After heating on a steam-bath for 3 hours, the mixture was filtered and the residue washed with fresh benzene. The combined filtrate and washings were shaken with excess 2*N* - sodium hydroxide and the aqueous layer was removed. The benzene layer was dried over solid potassium carbonate, filtered, and evaporated. The residue was distilled *in vacuo* to give 1 - *p*-methylbenzylamino - 2 - phenoxyethane, b.p. 138—142°/0.06 mm.

This base (13 g.) was added to a mixture of formic acid (98%; 6.0 ml.) and formalin (5.5 ml.; 37% w/w) with cooling. The final mixture was heated on a steam-bath for 8 hours, cooled, treated with concentrated hydrochloric acid (8 ml.), and evaporated *in vacuo*. Excess aqueous ammonia was added to the residue, the precipitated oil collected in ether, and the ethereal solution dried over solid potassium carbonate, filtered, and evaporated. The residue was distilled *in vacuo* to give 1 - *N*-methyl - *N* - *p* - methylbenzylamino - 2-phenoxyethane, b.p. 124—128°/0.04 mm.

Methyl iodide (3 g.) was added to a solution of this base (5.5 g.) in methanol (10 ml.) and the mixture heated to reflux for 1 hour. Addition of ether gave *N,N* - dimethyl - *N* - *p* - methylbenzyl - *N* - 2 - phenoxyethylammonium iodide which was recrystallised from ethanol, and then had m.p. 132—133°.

EXAMPLE 267.

By methods as described in Example 266, 1 - bromo - 2 - phenoxyethane and *p* - methoxybenzylamine were reacted together to give 1 - *p* - methoxybenzylamino - 2 - phenoxyethane, b.p. 145—148°/0.06 mm. This base (4.5 g.) was added to a slurry of anhydrous sodium carbonate (4.5 g.) in acetone (10 ml.) and was followed by methyl iodide (7 ml.). The mixture was heated to reflux for 1 hour and filtered whilst still hot. Addition of ether to the filtrate gave *N* - *p* - methoxybenzyl - *N,N* - dimethyl - *N* - 2 - phenoxyethylammonium iodide which was recrystallised from a mixture of acetone and ether, m.p. 108—109°.

EXAMPLE 268.

By a method analogous to that of Example 267 starting with 1 - bromo - 2 - phenoxyethane and *p* - butoxybenzylamino - 2 - phenoxyethane, *N* - *p* - butoxybenzyl - *N,N* - dimethyl - *N* - 2 - phenoxyethylammonium iodide was prepared as a colourless crystalline solid, m.p. 77—79°.

EXAMPLE 269.

A suspension of *N* - 2 - *p* - acetamidophenoxyethyl - *N* - *p* - chlorobenzyl - *N,N* - dimethylammonium chloride (13 g.) (Example 168) in methanol (100 ml.) was saturated with hydrogen chloride and the solution was heated to reflux for 3 hours. Evaporation of the mixture gave a gum which solidified on grinding with ethyl acetate. This *N* - 2 - *p* - aminophenoxyethyl - *N* - *p* -

chlorobenzyl - *N,N* - dimethylammonium chloride hydrochloride was recrystallised from ethanol, and by using a bath preheated to 140°, its melting points was found to be 172—174°. A solution of this solid in water was treated with ammonia until the pH was 8—9, and potassium iodide was then added to give *N* - 2 - *p* - aminophenoxyethyl - *N* - *p* - chlorobenzyl - *N,N* - dimethylammonium iodide which, after recrystallisation from isopropanol, had a melting point of 163—164°.

EXAMPLE 270.

m - Chlorobenzyl chloride (9.6 g.) was added to a slurry of potassium iodide (9.8 g.) in methanol (25 ml.), and then 1 - dimethylamino - 2 - phenoxyethane (8.2 g.) was added. There was a vigorous spontaneous reaction. After 15 minutes had elapsed, the mixture was heated on a steam-bath for 1 hour and then filtered. Addition of ether to the filtrate gave a gum which rapidly solidified. This *N* - *m* - chlorobenzyl - *N,N* - dimethyl - *N* - 2 - phenoxyethylammonium iodide was filtered off and, after recrystallisation from ethanol, had a melting point of 125—126°.

EXAMPLE 271.

By methods analogous to those of Example 270, *m* - nitrobenzyl chloride was reacted with 1 - dimethylamino - 2 - phenoxyethane in the presence of potassium iodide to yield *N,N* - dimethyl - *N* - *m* - nitrobenzyl - *N* - 2 - phenoxyethylammonium iodide, m.p. 169—170°, after recrystallisation from methanol.

EXAMPLE 272.

1 - Bromo - 2 - *m* - methylphenoxyethane (43 g.) was added to a solution of benzylamine (50 g.) in benzene and the mixture was heated on a steam-bath for 4 hours. After cooling, the insoluble solid was filtered off and washed with fresh benzene. The combined filtrate and washings were shaken with excess 4*N* - sodium hydroxide; the aqueous layer was removed and the residual benzene layer was dried over solid potassium hydroxide, filtered, and evaporated. The residue was distilled *in vacuo* to give 1 - benzylamino - 2 - *m* - methylphenoxyethane, b.p. 134—145°/0.5 mm.

This base (13 g.) was slowly added to a cooled mixture of formic acid (98%; 7 ml.) and formalin (35% w/v; 6.8 ml.). The final mixture was heated on a steam-bath for 8 hours, treated with concentrated hydrochloric acid (8 ml.), and then evaporated *in vacuo*. The 1 - (*N* - benzyl - *N* - methylamino) - 2 - *m* - methyl - phenoxyethane was liberated with ammonia and isolated with ether as a colourless liquid, b.p. 138—142°/0.08 mm.

This base (2 g.) was dissolved in acetone (10 ml.), and methyl iodide (2 g.) was added. After 4 hours, ethyl acetate was added to incipient cloudiness, when *N* - benzyl - *N* - 2 - *m* - methylphenoxyethyl - *N,N* - dimethylammonium iodide slowly crystallised. It was

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collected and recrystallised from a mixture of acetone and ether, as a solid of m.p. 107—108°.

EXAMPLE 273.

- 5 A solution of 1 - *p* - acetamidophenoxy-
2 - bromoethane (20 g.) and benzylmethyl-
amine (36 g.) in benzene (40 ml.) was heated
at reflux for 3 hours. After cooling, the se-
10 parated solid was filtered off and washed with
benzene. The combined filtrate and wash-
ings were extracted with excess 2*N* - hydro-
chloric acid. Basification of the extract with
excess ammonia gave 1 - *p* - acetamido-
15 phenoxy - 2 - (*N* - benzyl - *N* - methyl-
amino)ethane as an oil, which subsequently
crystallised. It was collected and recrystal-
lised from aqueous methanol or a mixture of
ethyl acetate and light petroleum (b.p. 40—
20 60°), and melted at 62—64°, clearing at 72°.

- This base (11 g.) was reacted with methyl
iodide (8 g.) in acetone (40 ml.) to give *N*-
2 - *p* - acetamidophenoxyethyl - *N* - benzyl-
N,N - dimethylammonium iodide, m.p. 230—
231°.

EXAMPLE 274.

- 25 Hydrogen chloride was passed into a sus-
pension of *N* - 2 - *p* - acetamidophenoxy-
ethyl - *N* - benzyl - *N,N* - dimethyl-
ammonium iodide (8 g.) (Example 272) in
30 methanol (80 ml.) to saturation. The solu-
tion was heated to reflux for 6 hours. Evapora-
tion then gave a gum which crystallised on
boiling with ethanol. The solid was collected
and recrystallised by precipitation from hot
35 methanol with ether to give *N* - 2 - *p* - amino-
phenoxyethyl - *N* - benzyl - *N,N* - dimethyl-
ammonium chloride hydrochloride m.p. 229—
230°.

EXAMPLE 275.

- 40 Ethylene glycol (20 ml.) was added to a
solution of sodium (2.3 g.) in ethanol (30 ml.)
and the ethanol evaporated *in vacuo*. *o*-
Bromobenzyl bromide (26.5 g.) was added

dropwise with stirring during 30 minutes,
and the mixture was heated on a steam-bath 45
with stirring for a further hour. Addition of
acetone precipitated sodium bromide; the
filtered solution was evaporated and the resi-
due distilled to give 1 - *o* - bromobenzyl-
2 - hydroxyethane, b.p. 99—106°/0.1 mm. 50

Thionyl chloride (4.9 ml.) in chloroform
(5 ml.) was slowly added to a mixture of
this ether (15.5 g.) and dimethylaniline (8.3
g.), below 30°. The mixture was heated on
the steam-bath for 30 minutes, cooled, and 55
poured into excess dilute hydrochloric acid.
Extraction with chloroform, washing the solu-
tion with dilute acid and with water, evapora-
tion, and distillation yielded 1 - *o* - bromo-
benzyloxy - 2 - chloroethane, b.p. 93—96°/
0.2 m.m. 60

A mixture of 1 - *o* - bromobenzyl-
2-chloroethane (12.35 g.) and dimethylamine
(40 ml.) of a 50% methanolic solution) was
heated in an autoclave at 80° for 3 hours. 65
After evaporation, the residue was dissolved
in dilute hydrochloric acid, and the solution
was washed with ether. Basification, extrac-
tion with chloroform, and distillation afforded
2 - *o* - bromobenzyl-2-chloroethyldimethylamine,
b.p. 92—97°/0.3 m.m. 70

A solution containing *p* - chlorobenzyl
chloride (4.1 g.) and sodium iodide (3.8 g.) in
acetone (75 ml.) was boiled under reflux for
30 minutes. After cooling and filtration, 2-
75 *o* - bromobenzyl-2-chloroethyldimethylamine (3.3
g.) was added, and the whole boiled for a
further 2 hours. Cooling and addition of
ether precipitated *N* - 2 - *o* - bromobenzyl-
oxyethyl - *N* - *p* - chlorobenzyl - *N,N* - di-
80 methylammonium iodide, which crystallised
from ethanol in colourless plates, m.p. 149—
152°.

EXAMPLE 276.

Granules were prepared from the follow- 85
ing ingredients:

N-p-chlorobenzyl-*N*-2-*p*-chlorobenzyl-2-chloroethyldimethylamine:—

<i>N,N</i> -dimethylammonium iodide (Example 140)	87.8% by weight
Cetrimide, as a dispersing agent	0.3% by weight
Lactose, as an inert diluent	11.2% by weight
Sodium saccharin	0.7% by weight

- 90 The sodium saccharin was mixed with the
lactose, and the iodide added. The mixture
was granulated with the cetrimide in ethanol.
The granules were sifted, dried and again
sifted.

The granules were suitable for oral ad-
ministration in water, by stirring, in a syrup
by trituration or in hard or soft gelatin 95
capsules.

EXAMPLE 277.

Tablets were prepared from the following ingredients:

N-p-chlorobenzyl-*N*-2-*p*-chlorobenzoyloxyethyl:—

<i>N,N</i> -dimethylammonium iodide (Example 140)	200 mg.
Lactose, as an inert diluent	200 mg.
Starch, as a binding agent	20 mg.
Magnesium stearate, as a lubricating agent	4 mg.

5 The iodide was triturated with the finely powdered lactose and the starch, in an atmosphere of low humidity. The powdered mixture was moistened with a granulating solution of gelatin in 50% ethanol and the materials kneaded together till a firm mass was obtained. The mass was sifted and dried at a temperature not exceeding 50°. The dried granules were sifted, mixed with the magnesium stearate and compressed into tablets in the usual way.

15 The tablets were suitable for sugar-coating with shellac followed by a sugar solution or for enteric coating with cellulose acetate phthalate.

EXAMPLE 278.

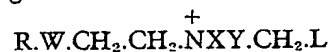
20 Similar preparations to those in Examples 276 and 277 were made of:

- a) *N* - *p* - chlorobenzyl - *N,N* - dimethyl-*N* - 3 - phenoxypropylammonium iodide (Example 232);
- 25 b) *N* - 4 - benzyloxybutyl - *N* - *p* - cyano-benzyl - *N,N* - dimethylammonium iodide (Example 245);
- c) *N* - 6 - *p* - bromophenoxyhexyl - *N* - *p*-chlorobenzyl - *N,N* - dimethylammonium chloride (Example 81);
- 30 d) *N* - 5 - *p* - bromophenoxy - 3 - oxapentyl-*N,N* - dimethyl - *N* - *p* - nitrobenzyl-ammonium chloride (Example 67);
- 35 e) *N* - 6 - *p* - bromophenoxyhexyl - *N* - *o*-chlorobenzyl - *N,N* - dimethylammonium chloride (Example 97);
- f) *N* - benzyl - *N* - 5 - *p* - bromophenoxy-3 - oxapentyl - *N,N* - dimethyl chloride (Example 128);
- 40 g) *N* - benzyl - *N,N* - dimethyl - *N* - 5 - *p*-nitrophenoxypentylammonium bromide (Example 54);
- 45 h) *N* - 5 - chlorothenyl - *N,N* - diethyl - *N*-3 - *p* - nitrophenoxypentylammonium iodide (Example 258); and
- i) *N* - *o* - chlorobenzyl - *N,N* - dimethyl-*N* - 3 - *p* - nitrophenoxypentylammonium oxide (Example 44).

50 WHAT WE CLAIM IS:—

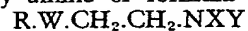
1. A method for the preparation of quaternary ammonium compounds characterised in that there are prepared compounds

containing a cation of the formula:



55 wherein R is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy-carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring optionally substituted in the *ortho*, *meta*, or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group, or when L is a thienyl or furyl group optionally substituted in the 5- position with a halogen atom or a nitro group; or R is a phenyl ring optionally substituted in the *ortho* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy-carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group; W is a straight saturated chain which contains 1 to 3 non-adjacent oxygen atoms and 0 to 16 carbon atoms; and X and Y are the same or different and each is an alkyl or allyl, group or XY is a tetramethylene, pentamethylene, or 3 - oxapentamethylene group, and wherein "alkyl," "alkoxy," and "alkoxy-carbonyl," denote respectively saturated hydrocarbon, ether, and ester groups containing from one to four carbon atoms, other than compounds containing an *N* - 5 - *p* - chlorophenoxy - 3 - oxapentyl - *N* - *p* - chlorobenzyl - *N,N* - dimethylammonium, *N* - *p* - *t* - butylphenoxy-ethoxyethyl - *N* - benzyl - *N,N* - dimethylammonium, *N* - benzyl - *N* - 5 - *p* - methylphenoxy - 3 - oxapentyl - *N,N* - dimethylammonium, *N* - benzyl - *N,N* - diethyl - *N*-2 - *m* - methoxyphenoxyethylammonium, or *N* - benzyl - *N,N* - diethyl - *N* - 2 - *m*-butoxyethylammonium cation; by a method comprising the reaction of a tertiary amine with a reactive ester of the hydroxy derivative of the group it is desired to introduce.

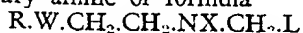
2. A method as claimed in claim 1 characterised in that it comprises the reaction of a tertiary amine of formula



100 with a reactive benzyl-, furfuryl- or thenyl-ester derivative.

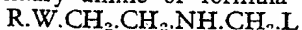
3. A method as claimed in claim 1 characterised in that it comprises the reaction of a tertiary amine of formula $XYN.CH_2.L$ with a reactive $R.W.CH_2.CH_2-$ ester derivative.

4. A method as claimed in claim 1 characterised in that it comprises the reaction of a tertiary amine of formula



with an alkylating agent.

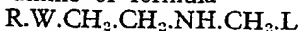
5. A method as claimed in claim 1 characterised in that it comprises the reaction of a secondary amine of formula



with two equivalents of an alkylating agent.

6. A method as claimed in claim 1 characterised in that it comprises the intramolecular quaternisation of a tertiary amine of formula $R.W.CH_2.CH_2.N[XY.Z]CH_2.L$, wherein Z is a reactive ester group.

7. A method as claimed in claim 1 characterised in that it comprises the reaction of a secondary amine of formula



with an α,ω -disubstituted butane, pentane or 3-oxapentane.

8. A method as claimed in any of claims 1 to 7 characterised in that the salt produced is converted into the salt of another anion so chosen as to give a salt which is sparingly soluble in water.

9. A method as claimed in any of claims 1 to 8 characterised in that there are prepared compounds containing a cation of the formula as defined in claim 1 wherein R is a *para*-bromophenyl ring.

10. A method as claimed in any of claims 1 to 8 characterised in that there are prepared compounds containing a cation of the formula as defined in claim 1 wherein R is a *para*-nitrophenyl ring.

11. A method as claimed in any of claims 1 to 8 characterised in that there are prepared compounds containing a cation of the formula as defined in claim 1 wherein R is a *para*-chlorophenyl ring and W contains only one oxygen atom.

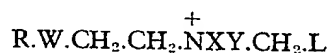
12. A method for making a pharmaceutical composition which comprises the inclusion of a quaternary ammonium compound, containing a cation of the formula:



wherein R is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring optionally substituted in the *ortho*, *meta*, or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group, or when L is a thienyl or furyl group optionally substituted in the 5-position with a halogen atom or a

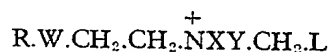
nitro group; or R is a phenyl ring optionally substituted in the *ortho* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group; W is a straight saturated chain with contains 1 to 3 non-adjacent oxygen atoms and 0 to 16 carbon atoms; and X and Y are the same or different and each is an alkyl or allyl group, or XY is a tetramethylene, pentamethylene, or 3-oxapentamethylene group, and wherein "alkyl," "alkoxy," and "alkoxy carbonyl" denote respectively saturated hydrocarbon, ether, and ester groups containing from one to four carbon atoms: in a pharmaceutically acceptable carrier therefor.

13. A pharmaceutical composition containing a quaternary ammonium compound, containing a cation of the formula:



wherein R is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring optionally substituted in the *ortho*, *meta*, or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group, or when L is a thienyl or furyl group optionally substituted in the 5-position with a halogen atom or a nitro group; or R is a phenyl ring optionally substituted in the *ortho* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy carbonyl, amino, acetamido, cyano, or nitro group, when L is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group; W is a straight saturated chain which contains 1 to 3 non-adjacent oxygen atoms and 0 to 16 carbon atoms; and X and Y are the same or different and each is an alkyl or allyl group, or XY is a tetramethylene, pentamethylene, or 3-oxapentamethylene group; and wherein "alkyl," "alkoxy," and "alkoxy carbonyl" denote respectively saturated hydrocarbon, ether, and ester groups containing from one to four carbon atoms; and a pharmaceutically acceptable carrier therefor.

14. A quaternary ammonium compound containing a cation of the formula:



wherein R is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, hydroxy, formyl, acetyl, alkoxy carbonyl, amino, acetamido, cyano, or

- nitro group, when L is a phenyl ring optionally substituted in the *ortho*, *meta*, or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group, or when L is a thienyl or furyl group optionally substituted in the 5-position with a halogen atom or a nitro group; or R is a phenyl ring optionally substituted in the *ortho* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group, when L is a phenyl ring substituted in the *meta* or *para* position with a halogen atom or an alkyl, alkoxy, cyano, or nitro group; W is a straight saturated chain which contains 1 to 3 non-adjacent oxygen atoms and 0 to 16 carbon atoms; and X and Y are the same or different and are each an alkyl or allyl group, or XY is a tetramethylene, pentamethylene, or 3-oxapentamethylene group; and wherein "alkyl," "alkoxy," and "alkoxycarbonyl" denote respectively saturated hydrocarbon, ether, and ester groups containing from one to four carbon atoms; other than compounds containing an N - 5 - p - chlorophenoxy - 3-oxapentyl - N - p - chlorobenzyl - N,N - dimethylammonium, N - p - t - butylphenoxyethoxyethyl - N - benzyl - N,N - dimethylammonium, N - 5 - p - methylphenoxy - 3-oxapentyl - N - benzyl - N,N - dimethylammonium, N - benzyl - N,N - diethyl - N - 2 - m - methoxyphenoxyethylammonium, or N - benzyl - N,N - diethyl - N - 2 - m - butoxyphenoxyethylammonium cation.
15. A quaternary ammonium compound containing a cation of the formula defined in claim 1 wherein the anion is so chosen as to give a salt which is sparingly soluble in water.
16. A quaternary ammonium compound containing a cation as defined in claim 14 wherein R is a *para*-bromophenyl ring.
17. A quaternary ammonium compound containing a cation as defined in claim 14 wherein R is *para*-nitrophenyl ring.
18. A quaternary ammonium compound containing a cation as defined in claim 14 wherein R is a *para*-chlorophenyl ring and W contains only one oxygen atom.
19. A quaternary ammonium compound containing the N - 2 - p - bromophenoxyethyl - N - 5 - chlorothenylpiperidinium cation.
20. A quaternary ammonium compound containing the N - 2 - p - bromophenoxyethyl - N - p - chlorobenzyl N,N - dimethylammonium cation.
21. A quaternary ammonium compound containing the N - 2 - p - bromophenoxyethyl - N - p - chlorobenzyl - pyrrolidinium cation.
22. A quaternary ammonium compound containing the N - p - bromobenzyl - N - 2 - p - bromophenoxyethyl - N,N - dimethylammonium cation.
23. A quaternary ammonium compound containing the N - 2 - p - bromophenoxyethyl - N - p - cyanobenzyl - N,N - dimethylammonium cation.
24. A quaternary ammonium compound containing the N - benzyl - N,N - diethyl - N - 2 - p - nitrophenoxyethyl - ammonium cation.
25. A quaternary ammonium compound containing the N - benzyl - N,N - dimethyl - N - 5 - p - nitrophenoxypentyl - ammonium cation.
26. A quaternary ammonium compound containing the N - 5 - chlorothenyl - N - 3 - p - nitrophenoxypropyl - pyrrolidinium cation.
27. A quaternary ammonium compound containing the N - p - chlorobenzyl - N,N - diethyl - N - 2 - p - nitrophenoxyethyl - ammonium cation.
28. A quaternary ammonium compound containing the N - p - chlorobenzyl - N,N - dimethyl - N - 4 - p - nitrophenoxybutyl - ammonium cation.
29. A quaternary ammonium compound containing the N - p - chlorobenzyl - N,N - diethyl - N - 3 - p - nitrophenoxypropyl - ammonium cation.
30. A quaternary ammonium compound containing the N - p - bromobenzyl - N,N - dimethyl - N - 3 - p - nitrophenoxypropyl - ammonium cation.
31. A quaternary ammonium compound containing the N - p - bromobenzyl - N - 3 - p - nitrophenoxypropylpyrrolidinium cation.
32. A quaternary ammonium compound containing the N - o - chlorobenzyl - N - 2 - p - chlorophenoxyethyl - N,N - dimethyl - ammonium cation.
33. A quaternary ammonium compound containing the N - o - chlorobenzyl - N - 2 - p - chlorophenoxyethyl - piperidinium cation.
34. A quaternary ammonium compound containing the N - benzyl - N - 2 - p - chlorophenoxyethyl - N,N - diethylammonium cation.
35. A quaternary ammonium compound containing the N - benzyl - N - 2 - p - chlorobenzyl - N,N - dimethylammonium cation.
36. A quaternary ammonium compound containing the N - p - chlorophenoxyethyl - N - 5 - chlorothenyl - N,N - diethyl - ammonium cation.
37. A quaternary ammonium compound containing the N - p - chlorobenzyl - N - 2 - p - chlorophenoxyethyl - N,N - dimethyl - ammonium cation.
38. A quaternary ammonium compound containing the N - 2 - p - chlorobenzyl - N - p - cyanobenzyl - N,N - dimethylammonium cation.
39. A quaternary ammonium compound containing the N - 5 - chlorothenyl - N,N - dimethyl - N - 3 - p - nitrophenoxypropyl - ammonium cation.
40. A quaternary ammonium compound

- containing the *N* - 5 - chlorothenyl - *N,N*-dimethyl - *N* - 4 - *p* - nitrophenoxybutyl-ammonium cation.
- 5 41. A quaternary ammonium compound containing the *N* - *p* - bromobenzyl - *N,N*-diethyl - *N* - 3 - *p* - nitrophenoxypropyl-ammonium cation.
- 10 42. A quaternary ammonium compound containing the *N* - *p* - chlorobenzyl - *N* - 3 - *p* - nitrophenoxypropylpyrrolidinium cation.
43. A quaternary ammonium compound containing the *N* - 3 - *p* - bromophenoxypropyl - *N* - *p* - chlorobenzyl - pyrrolidinium cation.
- 15 44. A quaternary ammonium compound containing the *N* - *p* - nitrobenzyl - *N* - 2 - *p* - nitrophenoxyethylpyrrolidinium cation.
45. A quaternary ammonium compound containing the *N* - *p* - chlorobenzyl - *N* - 2 - *p* - chlorophenoxyethyl - pyrrolidinium cation.
- 20 46. A quaternary ammonium compound containing the *N* - *p* - chlorobenzyl - *N,N*-dimethyl - *N* - 3 - *p* - nitrophenoxypropyl-ammonium cation.
47. A quaternary ammonium compound containing the *N,N* - dimethyl - *N* - *p*-iodobenzyl - *N* - 3 - *p* - nitrophenoxypropyl-ammonium cation.
- 25 48. A method for the preparation of a quaternary ammonium compound containing a cation of the formula defined in claim 1 substantially as hereinbefore described with reference to any of the foregoing examples or any obvious chemical equivalent.
- 30 49. A quaternary ammonium compound containing a cation of the formula defined in claim 1 when prepared by a method of preparation substantially as herein described or ascertained or any obvious chemical equivalent.
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